VOLUME 24 · NUMBER 14 · MAY 10 2006

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Patterns of Cancer Incidence, Mortality, and Prevalence Across Five Continents: Defining Priorities to Reduce Cancer Disparities in Different Geographic Regions of the World

Farin Kamangar, Graça M. Dores, and William F. Anderson

From the Nutritional Epidemiology and Biostatistics Branches, Division of Cancer Epidemiology and Genetics; Office of Preventive Oncology, Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

Submitted December 6, 2005; accepted January 30, 2006.

Supported in part by the Intramural Research Program of the National Institutes of Health/National Cancer Institute (Bethesda, MD).

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Address reprint requests to William F. Anderson, MD, MPH, Descriptive Studies Section, Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Executive Plaza South, Room 8036, 6120 Executive Blvd, Rockville, MD 20852-7244; e-mail: wanderso@mail.nih.gov.

0732-183X/06/2414-2137/$20.00

DOI: 10.1200/JCO.2005.05.2308

ABSTRACT

Efforts to reduce global cancer disparities begin with an understanding of geographic patterns in cancer incidence, mortality, and prevalence. Using the GLOBOCAN (2002) and Cancer Incidence in Five Continents databases, we describe overall cancer incidence, mortality, and prevalence, age-adjusted temporal trends, and age-specific incidence patterns in selected geographic regions of the world. For the eight most common malignancies—cancers of lung, breast, colon and rectum, stomach, prostate, liver, cervix, and esophagus—the most important risk factors, cancer prevention and control measures are briefly reviewed.

In 2002, an estimated 11 million new cancer cases and 7 million cancer deaths were reported worldwide; nearly 25 million persons were living with cancer. Among the eight most common cancers, global disparities in cancer incidence, mortality, and prevalence are evident, likely due to complex interactions of nonmodifiable (ie, genetic susceptibility and aging) and modifiable risk factors (ie, tobacco, infectious agents, diet, and physical activity). Indeed, when risk factors among populations are intertwined with differences in individual behaviors, cultural beliefs and practices, socioeconomic conditions, and health care systems, global cancer disparities are inevitable. For the eight most common cancers, priorities for reducing cancer disparities are discussed.

J Clin Oncol 24:2137-2150.

INTRODUCTION

Cancer health disparities reflect differences in cancer incidence, mortality, and prevalence among different populations.[1] Although the term health disparities is primarily used in the United States and health inequalities in other parts of the world, both terms can be similarly defined to indicate a difference or dissimilitude.[2] Cancer incidence is defined as the number of new cancer cases occurring in a defined population within a specified period of time.[3] Incidence is determined by exposure to etiologic factors and individual susceptibility and may be further affected by screening practices, health care access, and quality of care. Cancer mortality is influenced by cancer incidence, individual biologic factors, tumor characteristics and stage at diagnosis, and response to available treatment. Cancer prevalence represents the disease burden in a population at a specific time and is related to survivability, with the most curable or clinically controllable cancers comprising those with the highest prevalence.

In this article, we provide an overview of worldwide cancer incidence, mortality, and prevalence, along with a more extensive discussion of the eight most common cancers in the world. To identify priorities to reduce the global cancer burden, we review established risk factors and existing cancer prevention and control strategies for the major cancer sites.

MATERIALS AND METHODS

Overall Incidence, Mortality, and 5-Year Prevalence

Data for overall annual cancer incidence, annual mortality, and 5-year prevalence were obtained from the GLOBOCAN database for the year 2002.[4] Incidence rates were derived from cancer registries that encompass national populations or samples of populations from selected regions. Cause-specific mortality data were derived from national registration information. All incidence and mortality rates were age standardized to the World Standard Population and expressed per 100,000 person-years (PY). Five-year prevalence was expressed as the number of individuals alive 5 years after a diagnosis of cancer. As an indirect measure of cancer survival, a mortality-to-incidence rate ratio (MR:IR) was calculated by dividing the mortality rate by the incidence rate; MR:IR approaching 1.0 suggests a limited survival.

To identify regional disparities, we used geographic categories defined in GLOBOCAN, including world, more-developed countries (all regions of

Europe, Australia, New Zealand, North America and Japan), and less-developed countries (all regions of Africa, Central America, South America, all regions of Asia except Japan, Caribbean, Melanesia, Micronesia, and Polynesia). We also defined the following five geographic areas: Africa (Eastern Africa, Middle Africa, Northern Africa, Southern Africa, and Western Africa); Asia (Eastern Asia, South-Eastern Asia, South Central Asia, and Western Asia); Oceania (Australia and New Zealand); Central/South America (Central America and South America); Europe (Eastern Europe, Northern Europe, Southern Europe, and Western Europe); and North America (Northern America).

Age-Specific Incidence Patterns

Age-specific cancer incidence rates in 5-year age groups were obtained from Cancer Incidence in Five Continents database (CI5VIII) and expressed per 100,000 PY.[5] Using CI5VIII, we defined geographic areas to best approximate the five geographic areas in GLOBOCAN, (ie, Africa, Asia, Oceania, Europe, and North America). More-developed countries included all regions of Europe, Australia, New Zealand, North America and Japan; whereas less-developed countries included all regions of Africa, Central America, South America, and all regions of Asia except Japan. Age-specific incidence rate figures were generated with S-Plus 6.1 software (Insightful Corporation, Seattle, WA) using a log-log scale, as originally described by Armitage and Doll.[6,7]

Temporal Trends

Temporal patterns in selected geographic areas were assessed using incidence data from CI5 I-VIII. Incidence rates were plotted on a log-linear scale by five 5-year time periods (1973 to 1977, 1978 to 1982, 1983 to 1987, 1988 to 1992, and 1993 to 1997) and expressed per 100,000 PY, as previously described.[8] Geographic areas in each continent, except Africa, were selected based on availability of data over the specified time periods, and case numbers. No data were available from Africa. Geographic areas selected were United States (Surveillance, Epidemiology, and End Results database, white and black), United Kingdom (South Thames), Australia (South), Japan (Osaka Prefecture), Singapore (Chinese), Costa Rica, and Columbia (Cali). Data from each time period were not available for all geographic regions.[9]

WORLDWIDE OVERALL CANCER INCIDENCE, MORTALITY, AND PREVALENCE

In 2002, there were an estimated 10,864,499 new cancer cases (excluding skin cancer) worldwide (Fig 1), with 44.9% (n = 4,878,952) in Asia, 26.0% (n = 2,820,771) in Europe, 14.5% (n = 1,570,520) in North America , 7.1% (n = 766,575) in Central/South America, 6.0% (n = 649,760) in Africa, and 1.0% (n = 103,725) in Oceania. In general, the distribution of cancer deaths paralleled the distribution of cancer incidence. The number of 5-year prevalent cancer cases was highest in Asia, Europe, and North America. Geographic variation in overall incidence and mortality at least partly reflected the relative frequency of site-specific cancers occurring in more-developed compared with less-developed parts of the world.[10]

Worldwide incidence and mortality of site-specific cancers are depicted in Figure 2. Cancers of the lung, stomach, colon and rectum, liver, and esophagus are associated with the highest incidence worldwide, in addition to sex-specific malignancies of the female breast, uterine cervix, and prostate. Whereas cancers of the female breast and prostate are among the most common worldwide, mortality rates are comparatively low, yielding a low MR:IR, consistent with favorable survival. In contrast, cancers of the lung, liver, and esophagus are associated with high MR:IR approaching 1.00, indicative of poor survival. To more closely examine disparities among different geographic regions, next we consider the most common cancer sites individually.

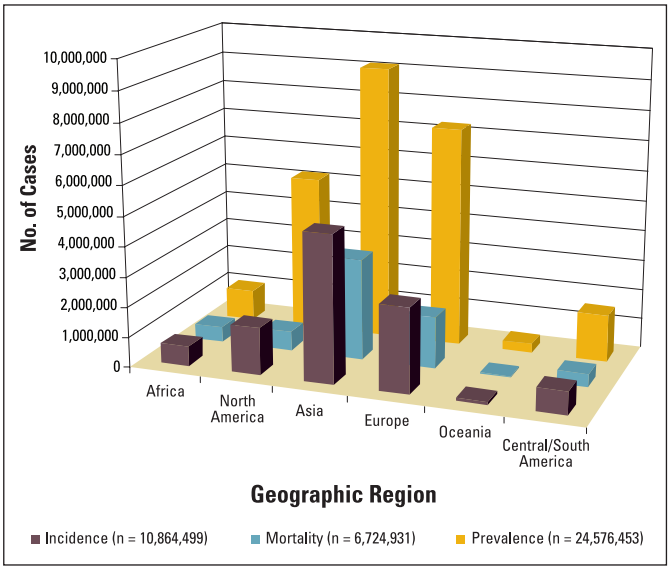

Fig 1. Worldwide overall annual cancer incidence, mortality, and 5-year prevalence (1993-2001).

Lung Cancer

With an estimated 965,446 new lung cancer cases per year among males and 386,875 cases per year among females, lung cancer is the most common cancer in the world and the leading cause of cancer-related mortality, accounting for 1,179,074 cancer deaths per year (Fig 2). During the years 1973 to 1997, lung cancer incidence rates either decreased or were stable among males in the geographic areas included in this study, except in Japan (Fig 3). In contrast, lung cancer rates generally increased among women in most regions (Fig 4), although this pattern may have moderated or ended in the late 1990s.[11]

Across continents, incidence rates varied from a low of 2.0 per 100,000 PY among females in Africa to a high of 61.2 per 100,000 PY among men in North America (Table 1). For both males and females, mortality rates were only slightly lower than incidence rates worldwide, yielding MR:IR ranging from 0.80 to 0.88. MR:IR rates were most favorable in North America and least favorable in Central/South America and Africa. Age specific incidence rate patterns were similar for both sexes in all parts of the world (Fig 5), increasing linearly with advancing age. Steadily rising age-specific incidence rates are consistent with long-term multistep carcinogenesis, purportedly requiring four to seven stochastic genetic changes over a lifetime of etiologic exposure.[12-14]

Cigarette smoking is by the far the most important risk factor for lung cancer.[15] Compared with nonsmokers, smokers have a 20-fold increased risk of developing lung cancer.[16] Other risk factors include occupational and indoor exposure to asbestos, radon progeny, and air pollution, as well as increasing age, genetic susceptibility, and perhaps low intake of fruits, vegetables, and micronutrients.[16-18]

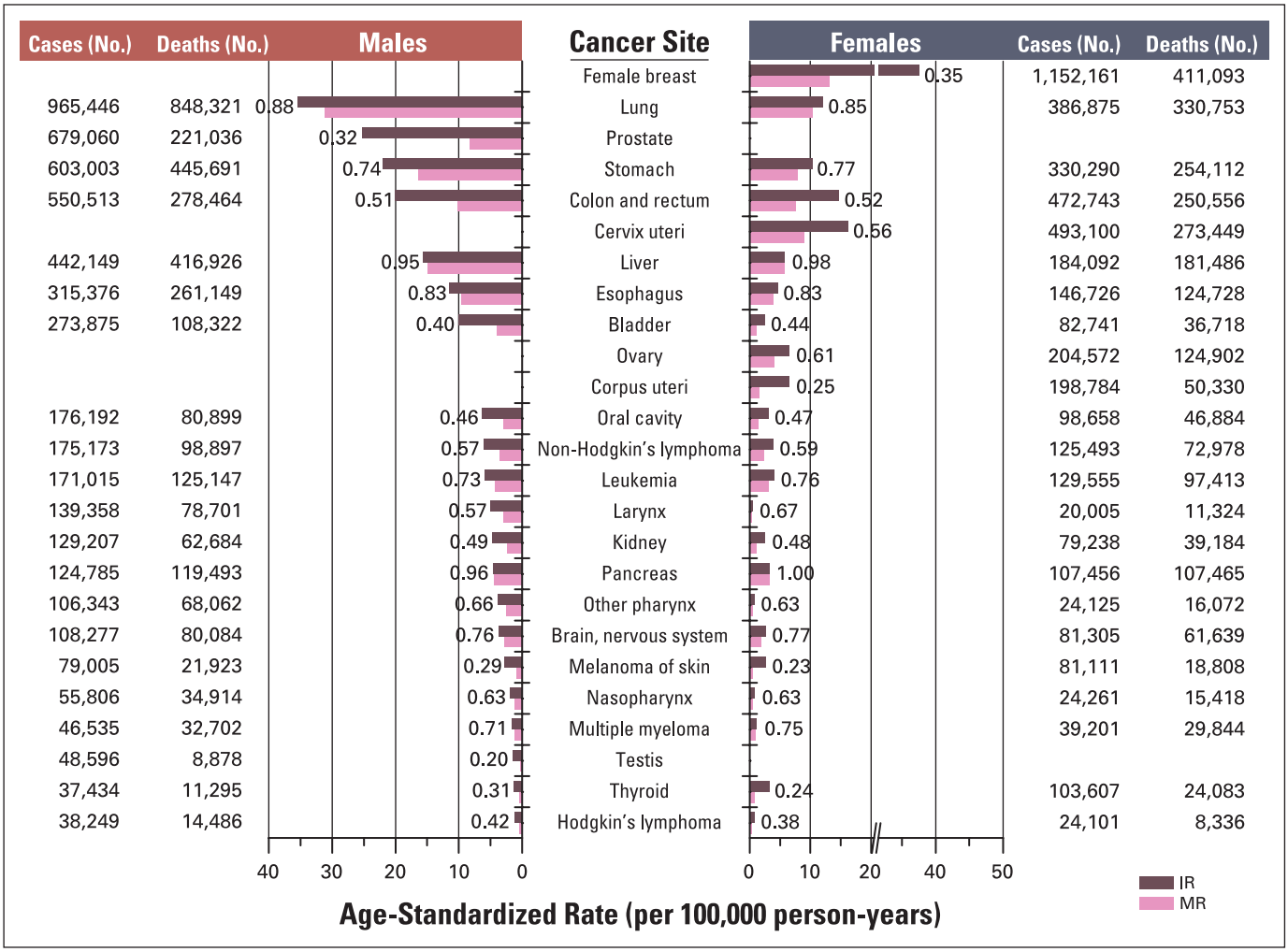

Fig 2. Worldwide annual number of cancer cases and cancer deaths, incidence rates (IRs), mortality rates (MRs), and mortality-to-incidence rate ratios (MR:IR; adjacent to bars) according to cancer site and sex (1993-2001). Reporting sources for IRs and MRs differ.

With a lag period of 20 to 30 years, patterns of lung cancer incidence closely follow smoking prevalence. Although lung cancer incidence currently is more common in the developed world, this pattern is expected to change in the next two decades. A dramatic rise in the incidence of lung cancer in China has been predicted, where smoking rates have markedly increased.[19] Estimates indicate that by 2030, 70% of tobacco-related deaths will occur in developing countries.[20]

Despite therapeutic advances, little gain has been achieved in overall lung cancer survival over the past 30 years, with approximately 15% 5-year survival rates for all stages combined.[21] Thus, conventional treatment remains an unsatisfactory means by which to decrease global lung cancer burden. Chemoprevention is theoretically possible for primary lung cancer prevention, although clinical trials have been disappointing to date.[22] Results from ongoing clinical trials to determine whether screening strategies will favorably impact lung cancer survival are awaited.[23]

Currently the most effective and important approach to reduce lung cancer burden worldwide is to reduce smoking rates through behavioral interventions and public health policy. Smoking cessation methods that are sensitive to country-specific needs and customs will be important to ensure successful outcomes.[20] To this end, in 2003 the World Health Assembly adopted the World Health Organization Framework Convention on Tobacco Control,[24] the first international treaty designed to enhance national and international coordination to control the tobacco epidemic. Entering into force in February 2005, the World Health Organization Framework Convention on Tobacco Control incorporates a variety of measures to counter the tobacco epidemic, including both concrete obligations or requirements and recommendations.[25] Requirements include restrictions on advertising, sponsorship, and promotion of tobacco products, and enforcement of packaging and labeling specifications. Recommendations include establishing clean indoor air controls and strengthening legislation against tobacco smuggling.

Female Breast Cancer

With an estimated 1,152,161 new cases each year, female breast cancer is the second most common cancer in the world and the most common cancer among women, accounting for 411,093 cancer deaths per year (Fig 2). Breast cancer incidence rates increased in all regions of the world included in this study during the years 1973 and 1997 (Fig 4), with the highest rates in Surveillance, Epidemiology, and

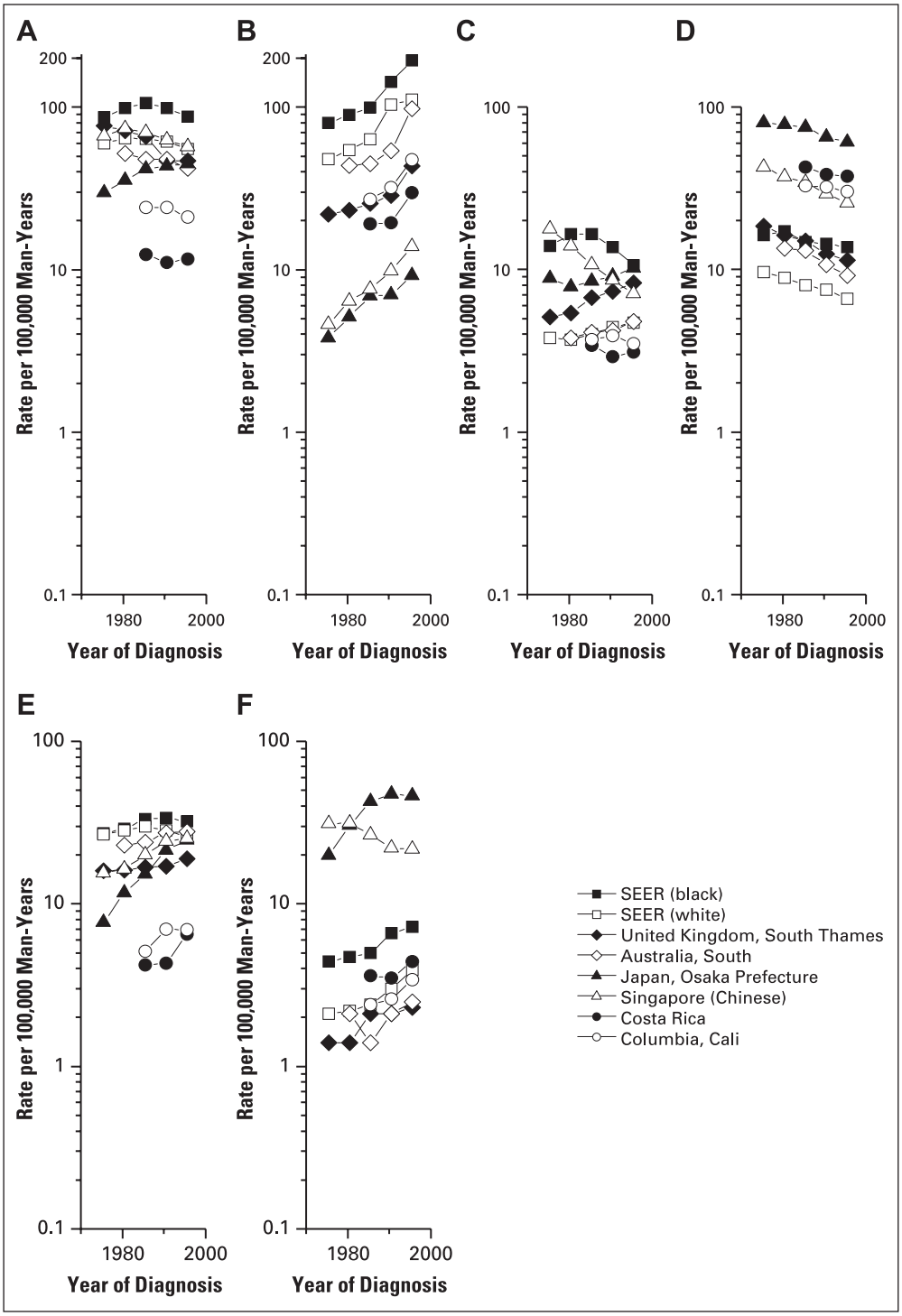

Fig 3. Age-standardized cancer incidence rates among males in various geographical areas according to specified cancer sites (1973-1997). (A) Lung; (B) prostate; (C) esophagus; (D) stomach; (E) colon; (F) liver. SEER, Surveillance, Epidemiology, and End Results database.

End Results (whites) and the lowest rates in Japan (Osaka Prefecture) and Costa Rica. Incidence rates were nearly three-fold higher in more-developed than less-developed geographic locations (67.8 to 23.8 per 100,000 PY; Table 1), whereas mortality rates were less than two-fold higher in more-developed than less-developed areas. Consequently, MR:IRs varied widely, from a low of 0.19 in North America to a high 0.69 in Africa.

Notwithstanding well-established reproductive risk factors such as early menarche, low parity, late age at first pregnancy, late menopause, and hormonal exposures,[26] the greatest risk factor for developing female breast cancer is aging.[27] However, while incidence rates for most epithelial cancers rise steadily with aging (Fig 5),[6,7] rates for female breast cancer increase rapidly until approximately age 50 years then rise more slowly. The midlife inflection in

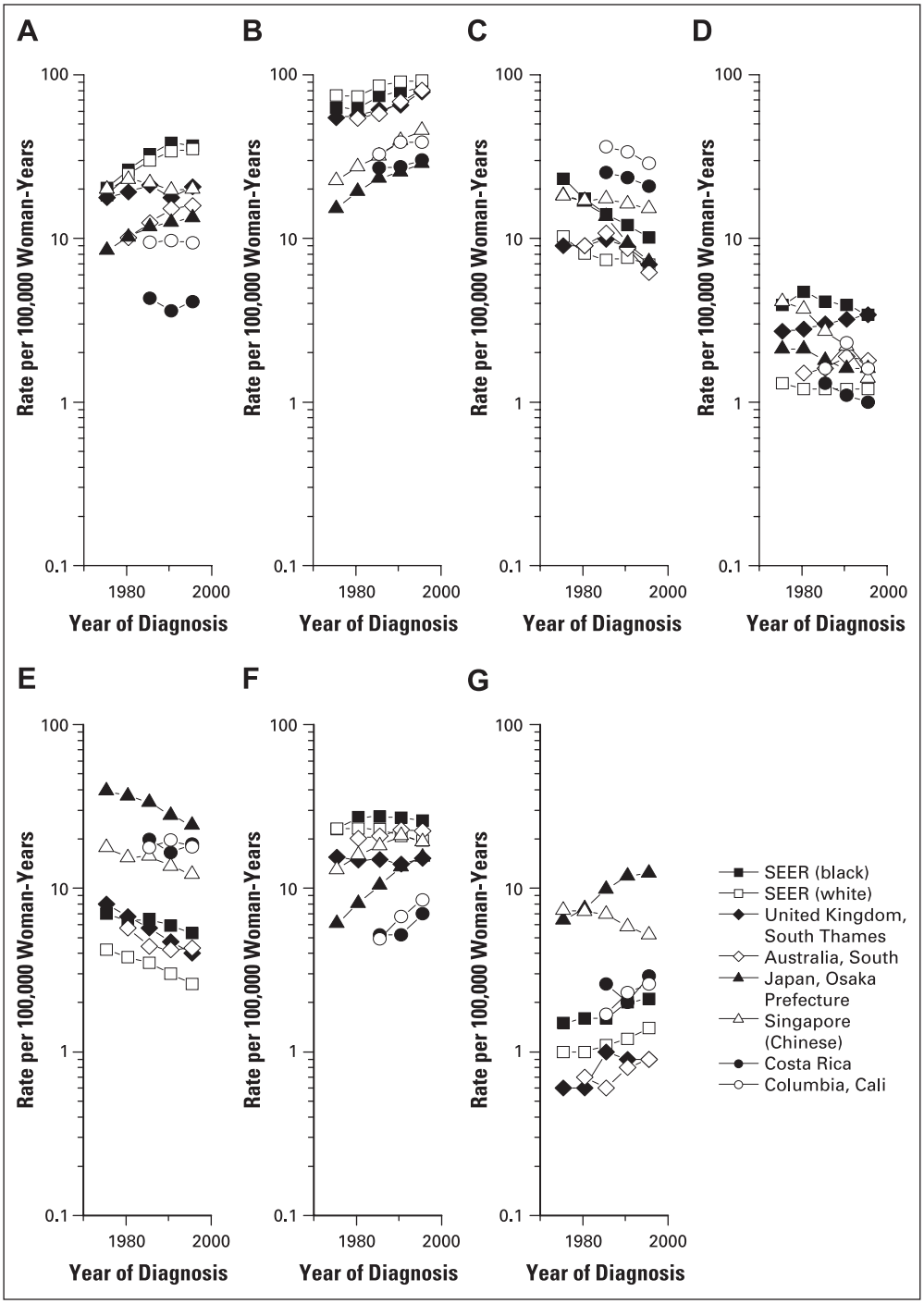

Fig 4. Age-standardized cancer incidence rates among females in various geographic areas according to specified cancer sites (1973-1997). (A) Lung; (B) breast; (C) cervix; (D) esophagus; (E) stomach; (F) colon; (G) liver. SEER, Surveillance, Epidemiology, and End Results database.

age-specific rates is termed Clemmesen's hook and has been attributed to menopause.[28-30]

Following Clemmesen's menopausal hook, breast cancer rate patterns among older women vary worldwide (Fig 5), continuing to rise more slowly in high-risk (or more-developed) areas and flattening or falling in low-risk (or less-developed) regions. Divergent age-specific rates after Clemmesen's hook have been attributed by some investigators to calendar-period and/or birth cohort artifacts,[31,32] whereas others have speculated the superimposition (or mixture) of two distinct rate patterns, corresponding to estrogen receptor (ER) -positive and ER-negative breast cancers.[33,34] Rates for ER-positive tumors increase rapidly until age 50 years then rise more slowly, similar to overall rates in high-risk countries. In contrast, rates for ER-negative tumors rise rapidly until age 50 years then plateau, similar to overall rates in low-risk countries.[34-36]

Accumulating molecular data also suggest the existence of two main breast cancer types according to ER expression.[37] Indeed, clinicians have long-suspected two types of breast cancer with age at onset being the major determinant of breast cancer outcome[38-41]; one type occurring in premenopausal women and characterized by aggressive

Table 1. Worldwide Age-Standardized Incidence Mortality Rates, and Mortality-to-Incidence Ratios for Selected Cancer Sites According to Sex (1993-2001)

	Males					Females				
	Incidence		Mortality			Incidence		Mortality		
Cancer	No.	Rate	No.	Rate	MR:IR*	No.	Rate	No.	Rate	MR:IR*
All sites, except skin										
World	5,802,531	209.6	3,796,383	137.7	0.66	5,061,968	161.5	2,928,548	92.2	0.57
More developed	2,698,175	314.1	1,503,060	169.6	0.54	2,317,939	228.0	1,185,412	102.5	0.45
Less developed	3,092,817	158.7	2,284,779	119.3	0.75	2,736,696	128.8	1,738,455	83.1	0.65
Continent										
North America	834,546	398.4	331,226	153.0	0.38	735,974	305.1	300,745	112.1	0.37
Oceania	56,119	349.7	24,812	149.1	0.43	47,606	280.3	19,611	103.4	0.37
Europe	1,499,642	290.7	958,248	180.8	0.62	1,321,129	209.7	743,224	103.6	0.49
Central/South America	365,497	198.9	221,243	122.6	0.62	401,078	182.2	215,395	99.2	0.54
Asia	2,697,813	167.0	1,983,473	124.3	0.74	2,181,139	126.1	1,372,455	79.9	0.63
Africa	311,363	126.0	251,099	104.1	0.83	338,397	121.0	255,013	92.6	0.77
Lung cancer										
World	965,446	35.5	848,321	31.2	0.88	386,875	12.1	330,753	10.3	0.85
More developed	481,950	54.9	423,507	47.6	0.87	194,731	17.0	161,472	13.6	0.80
Less developed	481,222	25.9	422,860	22.9	0.88	191,164	9.4	168,453	8.3	0.88
Continent										
North America	131,481	61.2	105,718	48.7	0.80	94,160	35.6	72,631	26.7	0.75
Oceania	6,539	39.1	5,848	34.7	0.89	3,285	17.4	2,820	14.6	0.84
Europe	296,364	56.8	270,832	51.1	0.90	78,396	11.3	70,765	9.8	0.87
Central/South America	38,587	21.8	35,615	20.3	0.93	15,646	7.3	15,291	7.2	0.99
Asia	472,791	30.1	411,414	26.3	0.87	188,559	11.0	162,648	9.5	0.86
Africa	14,752	7.0	14,172	6.7	0.96	4,776	2.0	4,559	1.9	0.95
Female breast cancer										
World	—	—	—	—	—	1,152,161	37.5	411,093	13.2	0.35
More developed	—	—	—	—	—	636,128	67.8	189,765	18.1	0.27
Less developed	—	—	—	—	—	514,946	23.8	221,028	10.4	0.44
Continent										
North America	—	—	—	—	—	229,631	99.4	48,239	19.2	0.19
Oceania	—	—	—	—	—	13,507	84.6	3,338	19.4	0.23
Europe	—	—	—	—	—	360,746	62.3	129,010	19.7	0.32
Central/South America	—	—	—	—	—	90,147	41.0	30,361	14.0	0.34
Asia	—	—	—	—	—	385,853	22.1	152,967	8.8	0.40
Africa	—	—	—	—	—	65,197	23.4	44,399	16.2	0.69
Colorectal cancer										
World	550,513	20.1	278,464	10.2	0.51	472,743	14.6	250,556	7.6	0.52
More developed	353,390	40.0	159,914	17.7	0.44	312,341	26.6	153,980	12.3	0.46
Less developed	196,093	10.2	118,042	6.2	0.61	159,730	7.7	96,222	4.7	0.61
Continent										
North America	94,745	44.4	33,421	15.3	0.34	88,728	32.8	32,939	11.6	0.35
Oceania	7,897	48.2	3,247	19.4	0.40	7,002	36.9	2,786	14.1	0.38
Europe	192,982	36.1	102,228	18.7	0.52	178,724	24.2	101,067	12.8	0.53
Central/South America	25,837	14.3	13,072	7.3	0.51	27,995	13.0	14,457	6.7	0.52
Asia	213,456	13.3	113,204	7.1	0.53	156,240	9.1	87,541	5.1	0.56
Africa	12,778	5.4	11,525	4.8	0.89	10,903	4.2	9,738	3.7	0.88
Stomach cancer										
World	603,003	22.0	445,691	16.3	0.74	330,290	10.3	254,112	7.9	0.77
More developed	195,782	22.3	128,721	14.5	0.65	115,372	10.0	83,515	6.9	0.69
Less developed	404,788	21.5	315,249	17.0	0.79	213,804	10.4	169,777	8.3	0.80
Continent										
North America	15,742	7.4	9,096	4.2	0.57	9,158	3.4	6,205	2.2	0.65
Oceania	1,632	9.9	1,005	6.0	0.61	828	4.2	603	3.0	0.71
Europe	104,620	20.0	83,280	15.7	0.79	69,394	9.5	57,626	7.6	0.80
Central/South America	39,480	22.0	29,400	16.5	0.75	25,597	11.8	19,528	9.0	0.76
Asia	425,146	26.9	307,755	19.6	0.73	211,520	12.3	157,340	9.2	0.75
Africa	13,836	6.2	13,002	5.8	0.94	12,350	4.9	11,633	4.6	0.94

(continued on following page)

Table 1. Worldwide Age-Standardized Incidence Mortality Rates, and Mortality-to-Incidence Ratios for Selected Cancer Sites According to Sex (1993-2001) (continued)

	Males					Females				
	Incidence		Mortality			Incidence		Mortality		
Cancer	No.	Rate	No.	Rate	MR:IR*	No.	Rate	No.	Rate	MR:IR*
Prostate cancer										
World	679,060	25.3	221,036	8.2	0.32	—	—	—	—	—
More developed	513,464	56.2	130,382	13.5	0.24	—	—	—	—	—
Less developed	165,401	9.4	90,550	5.2	0.55	—	—	—	—	—
Continent										
North America	257,943	119.9	36,447	15.8	0.13	—	—	—	—	—
Oceania	13,486	79.9	3,206	18.1	0.23	—	—	—	—	—
Europe	225,226	40.0	83,064	14.2	0.36	—	—	—	—	—
Central/South America	73,112	42.9	29,606	17.4	0.41	—	—	—	—	—
Asia	70,317	4.7	40,126	2.7	0.57	—	—	—	—	—
Africa	29,663	16.0	23,564	12.8	0.80	—	—	—	—	—
Liver cancer										
World	442,149	15.7	416,926	14.9	0.95	184,092	5.8	181,486	5.7	0.98
More developed	74,253	8.5	71,153	8.0	0.94	36,151	3.0	38,083	3.0	1.00
Less developed	365,923	18.4	343,956	17.4	0.95	147,210	7.1	142,728	6.9	0.97
Continent										
North America	11,058	5.3	9,229	4.4	0.83	5,152	1.9	5,319	1.9	1.00
Oceania	622	3.9	573	3.5	0.90	239	1.3	292	1.5	1.15
Europe	35,301	6.7	36,136	6.7	1.00	18,315	2.5	21,351	2.7	1.08
Central/South America	7,233	4.0	10,818	6.0	1.50	7,119	3.3	10,940	5.1	1.55
Asia	350,291	21.3	323,078	19.7	0.92	135,248	7.9	125,703	7.3	0.92
Africa	35,812	14.8	35,215	14.6	0.99	16,912	6.2	16,638	6.2	1.00
Cervical cancer										
World	—	—	—	—	—	493,100	16.2	273,449	9.0	0.56
More developed	—	—	—	—	—	83,437	10.3	39,512	4.0	0.39
Less developed	—	—	—	—	—	409,269	19.1	233,727	11.2	0.59
Continent										
North America	—	—	—	—	—	14,670	7.7	5,796	2.3	0.30
Oceania	—	—	—	—	—	1,063	7.4	330	2.0	0.27
Europe	—	—	—	—	—	59,931	11.9	29,812	5.0	0.42
Central/South America	—	—	—	—	—	65,493	29.0	29,524	13.4	0.46
Asia	—	—	—	—	—	265,744	15.4	142,679	8.4	0.55
Africa	—	—	—	—	—	78,897	29.3	61,671	23.1	0.79
Esophageal cancer										
World	315,376	11.5	261,149	9.6	0.83	146,726	4.7	124,728	3.9	0.83
More developed	57,889	6.8	50,295	5.8	0.85	15,986	1.3	14,827	1.2	0.92
Less developed	256,217	13.7	209,851	11.4	0.83	130,215	6.5	109,478	5.4	0.83
Continent										
North America	12,111	5.8	10,778	5.1	0.88	3,625	1.3	3,330	1.2	0.92
Oceania	905	5.5	801	4.8	0.87	465	2.3	370	1.8	0.78
Europe	33,070	6.5	29,659	5.7	0.88	9,970	1.3	9,474	1.2	0.92
Central/South America	10,479	5.9	9,631	5.4	0.92	3,748	1.8	3,516	1.7	0.94
Asia	241,301	15.3	193,465	12.4	0.81	120,443	7.1	99,908	5.9	0.83
Africa	16,289	7.8	15,659	7.5	0.96	8,058	3.4	7,743	3.2	0.94

NOTE. All rates are age standardized to the world population and expressed per 100,000 person-years.
Abbreviations: MR:IR, mortality-to-incidence rate ratio.
*MR:IR may exceed 1.00 because of different reporting sources for incidence and mortality rates.

and largely ER-negative features with a second type occurring in postmenopausal women and associated with indolent and mostly ER-positive features.

ER expression also varies by morphologic subtype of breast cancer.[42-45] For example, ER-negative tumors are most common in medullary breast carcinomas.[42] Notably, medullary carcinomas are rare tumors that have been associated with germline mutations in *BRCA1*,[46-61] and are more common in low-risk, native Japanese[35,44,62-65] and African[66] populations than in high-risk United States populations. On the other hand, tubular and lobular carcinomas have been associated with ER-positive breast cancers, germline mutations in *BRCA2*,[46,54,57,60,61] and are more common in high-risk populations such as the United States.[44,67]

A predominance of early-onset and aggressive ER-negative breast cancers in low-risk countries may, in part, account for the high MR:IR in less-developed regions such as Asia (0.40 per 100,000

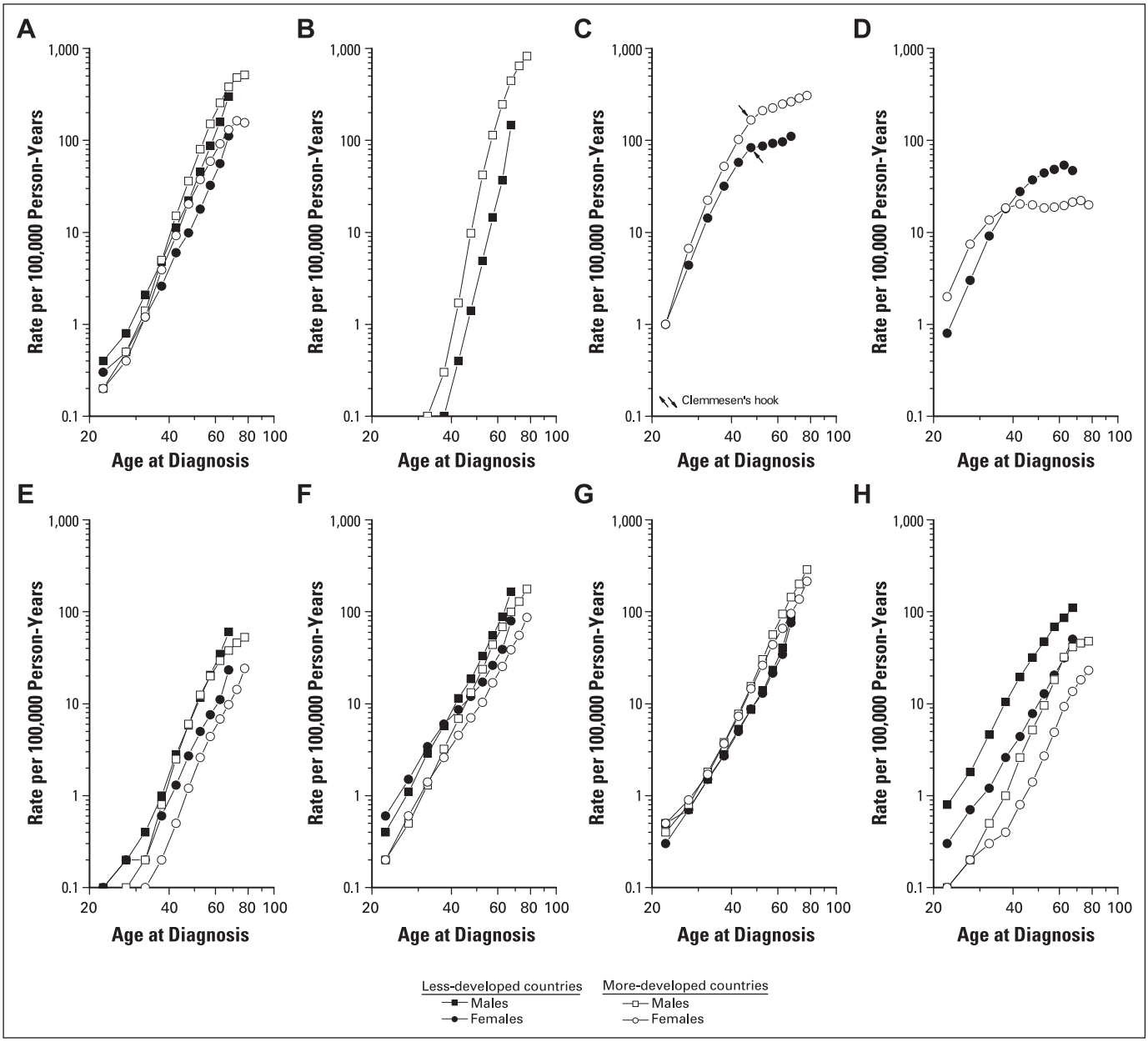

Fig 5. Age-specific cancer incidence rates in more-developed and less-developed countries according to specified cancer sites and sex, 1993-2001. (A) Lung; (B) prostate; (C) female breast; (D) cervix; (E) esophagus; (F) stomach; (G) colon; (H) liver. Incidence rates are age standardized to the world population.

person-years) and Africa (0.69 per 100,000 person-years; Table 1). In contrast, a larger fraction of late-onset and indolent ER-positive tumors in high-risk countries may explain the lower MR:IR in more-developed areas such as North America (0.19). In fact, Lawson et al[68] examined migration patterns according to ER expression between two populations with similar genetic background (ie, Japanese women from Hawaii and Japanese women from Sapporo, Japan.) Japanese women in Hawaii had higher breast cancer incidence and relatively more ER-positive tumors than native Japanese women, whereas native Japanese women had lower incidence but comparatively more ER-negative tumors, consistent with the hypothesis that ER-positive tumors are associated with geographic regions characterized by high breast cancer incidence rates.

Geographic disparities in breast cancer incidence and mortality are also related to differences in screening, chemoprevention, and treatment strategies in more-developed compared with less-developed regions of the world. Estimates from randomized clinical trials and population-based models from countries such as the United States and United Kingdom suggest that early detection and improved treatment might reduce breast cancer mortality rates by 25% to 30%.[69,70] Of note, differential detection of ER-positive tumors by screening mammography also accentuates disparities in breast cancer patterns, by yielding a higher incidence of more indolent tumors associated with more favorable survival.[71-73]

In sum, ER-negative and ER-positive breast cancers appear to be distinct breast cancer types with unique incidence and prognostic

patterns, molecular signatures, and morphologic features. With breast cancer screening detection rates, chemoprevention,[74] and treatment strategies[75] also varying by ER expression, a stratified breast cancer model may be an important conceptual framework to consider for reducing global breast cancer disparities.

Colorectal Cancer

Colorectal cancer (CRC) is the third most common cancer worldwide after lung and breast cancers, accounting for an estimated 1,023,256 new cancer cases and 529,020 cancer deaths per year (Fig 2). Between 1973 and 1997, colon cancer incidence rates increased in most parts of the world included in this study (Figs 3 and 4), except in the United States where incidence rates peaked in the mid-1980s and then began to decline.[76]

Among both men and women, incidence rates were nearly four-fold higher in more-developed compared with less-developed regions of the world (Table 1), whereas mortality rates were only two-and-a-half-fold higher. Across continents, MR:IRs were lowest in North America and highest in Africa, ranging from 0.34 in men in North America to 0.89 in men in Africa.

Colorectal carcinogenesis is a prototypical long-term multistep process with each step corresponding to key etiologic events.[6,7,14,77] Over a lifetime of accumulated carcinogenic events there is pathologic evolution from premalignant adenoma to invasive CRC. The adenoma-to-carcinoma (ACS) sequence results in a linear age-specific incidence rate pattern when rates are plotted on a log-log scale (Fig 5).

The complete ACS can take from 10 to 15 years or more.[78] During this time period, environmental exposures presumably promote the carcinogenic process, the latter also affected by individual genetic susceptibility. However, the dominant role of environmental risk factors in the ACS has been demonstrated in migrant studies, where CRC risk increases several fold among first generation immigrants emigrating from a country at low risk for developing CRC to one at high risk.[79,80] Consequently, there is a strong ecologic correlation between increased CRC incidence and dietary factors such as low fiber intake.[81] Some case-control and cohort studies have found modest associations (relative risks, < 2) between increased CRC risk and low intake of fiber and vegetables[82,83] and folate,[84] as well as high consumption of meat.[85,86] However, these relationships have been inconsistent across studies, and clinical trials thus far have failed to show a benefit for either dietary or supplemental fiber intake in reducing colorectal adenomas.[87] Closely related to dietary intake, excess body weight,[88,89] and physical inactivity[90,91] have also been linked with increased risk of CRC.

The decline in CRC rates during the 1980s and 1990s in the United States has been attributed to increasing CRC screening and therapeutic interventions, following President Ronald Reagan's diagnosis of CRC in 1985.[92] For all average risk individuals aged 50 years or older, the American Cancer Society currently recommends one of four routine CRC screening options: fecal occult blood testing (FOBT) every year; flexible sigmoidoscopy (FS) every 5 years; double contrast barium enema every five years; or colonoscopy every 10 years.[93]

The ultimate goal of CRC screening is to interrupt the ACS, and attempt to reduce CRC incidence and mortality. Annual home-based FOBT reduces CRC incidence by 20% and mortality by 16%.[94] FS directly visualizes the rectum and distal colon, but does not reach the proximal colon. Combined FOBT and FS are probably more effective than either test alone. In addition, colonoscopy performed in follow-up for abnormal FS yields a 40% to 80% reduction in CRC incidence.[95-99] Colonoscopy is the current gold standard for colorectal cancer screening and the preferred diagnostic test to pursue an abnormal CRC screening test. Despite widespread acceptance in the United States, CRC screening practices vary worldwide.[100]

Though not yet a clinical reality, chemopreventive agents targeting critical CRC pathways have successfully interrupted the ACS. Indeed, more than 40 candidate agents (nonsteroidal anti-inflammatory drugs, selenium, hormone replacement therapy, and calcium carbonate) show promise for CRC prevention.[101] However, given that chemopreventive agents are administered to ostensibly healthy individuals, the ultimate effectiveness of any agent will depend on establishing a favorable risk-to-benefit ratio. With the narrow therapeutic index for most chemopreventive agents, alone or in combination, the most effective strategies for reducing the worldwide CRC burden currently include primary prevention through modifiable risk factors and secondary prevention through screening.

Stomach Cancer

Stomach cancer is the fourth most common cancer worldwide, with 603,003 new cases among men and 330,290 new cases among women (Fig 2). Across continents, incidence rates vary from 3.4 per 100,000 PY among females in North America to 26.9 per 100,000 PY among males in Asia, whereas MR:IRs are consistently high in all parts of the world (Table 1). Overall 5-year relative survival rates approximate 20%[21,102,103] in most areas of the world, except in Japan where mass screening programs, staging systems, and treatment may contribute to superior 5-year survival rates of approximately 60%.[5,104,105]

Stomach cancers are anatomically classified as noncardia and cardia cancers. Because noncardia cancers constitute the majority of stomach cancer cases worldwide, overall stomach cancer incidence rates are predominated by this disease entity. Risk factors for noncardia cancers include *H pylori* infection,[106] low socioeconomic status,[107,108] smoking,[109] intake of salty and smoked food,[110,111] and low consumption of fruits and vegetables.[112] In the past century, the incidence of noncardia stomach cancer has declined several fold in more-developed regions of the world.[113] This decrease likely reflects a diminishing prevalence of *H pylori* infection due to improved sanitation, increasing availability of fresh fruits and vegetables, and decreasing use of salt- and smoke-based food preservation methods. However, noncardia stomach cancer remains common in many geographic regions, including China, Japan, Eastern Europe, and Central/South America.[113]

In contrast to noncardia cancers, incidence rates of gastric cardia cancers have either increased or remained constant in Western countries.[114-116] Risk factors for cardia cancer include male sex,[117] white race,[117] smoking,[118,119] obesity,[118,119] and gastroesophageal reflux.[120] The association between *H pylori* and cardia cancer is unclear.[121]

Major prevention strategies to reduce stomach cancer incidence include improved sanitation, higher intake of fresh fruits and vegetables, food preservation methods that are not salt- or smoke-based, avoidance of tobacco products, and maintenance of a normal body weight. To date there is insufficient clinical evidence to recommend endoscopic screening worldwide.

Prostate Cancer

Prostate cancer is the fifth most common cancer in the world and the second most common cancer among men (Fig 2). During the years 1973 to 1997, prostate cancer incidence rates increased in all parts of the world (Fig 3). Annual incidence rates were nearly six-fold higher in more-developed compared with less-developed regions (Table 1), ranging from 4.7 per 100,000 PY in Asia to 119.9 per 100,000 PY in North America. However, mortality rates were only 2.5 times higher in more-developed compared with less-developed parts of the world, and consequently MR:IRs ranged from 0.13 in North America to 0.80 in Africa. Age-specific incidence rates rose steadily with advancing age worldwide (Fig 5).

Diet has been implicated in the etiology of prostate cancer, but definitive etiologic evidence is lacking. High intake of animal fat,[122] meat,[122] and calcium[123] has been associated with an increased risk of prostate cancer, whereas high intake of vegetables,[123] selenium,[124,125] vitamin D,[126] vitamin E,[127,128] lycopene,[129] and omega-3 fatty acids[130] has been associated with reduced risk for prostate cancer. Obesity has been linked with increased risk of prostate cancer death.[131]

Differences in worldwide prostate cancer incidence rates may in part be due to variations in diet, but are also likely influenced by more vigorous screening with prostate-specific antigen testing in more-developed countries. Autopsy series have shown prostate cancer prevalence of approximately 80% in men who died in their 70s from other causes.[132,133] Therefore, prostate-specific antigen testing likely results in the detection of some biologically indolent prostate cancers. It is unclear whether superior survival in more-developed countries stems from earlier detection and improved treatment or reflects detection of biologically indolent disease. The United States Preventive Services Task Force finds insufficient evidence for prostate cancer screening.[134] However, additional evidence regarding screening recommendations is anticipated based on results from large randomized screening studies in both Europe and the United States.[135,136]

Based on current knowledge of risk factors, it is possible that a diet rich in intake of vegetables and low in meat and animal fat may reduce prostate cancer risk. Final disposition regarding the benefit of selenium and vitamin supplementation is pending completion of ongoing clinical trials, including National Cancer Institute–sponsored Selenium and Vitamin E Cancer Prevention Trial (SELECT).[137]

Liver Cancer

With 626,241 new cancer cases per year, liver cancer is the sixth most common cancer in the world. It is approximately 2.5 times more common among men than women (Fig 2). Between 1973 and 1997, incidence rates increased in all parts of the world included in this study, except Singapore (Figs 3 and 4). For both men and women, liver cancer incidence rates were higher in less-developed than more-developed regions (Table 1; Fig 5). Indeed, incidence rates ranged from 1.3 per 100,000 PY among females in Oceania to 21.3 per 100,000 PY among males in Asia. Survival is universally poor as reflected by MR:IRs approximating unity (Table 1).

The most important risk factors for liver cancer are hepatitis B virus (HBV),[138] hepatitis C virus (HCV),[139] and dietary aflatoxins.[140] Other well-established risk factors include alcoholic liver disease[141] and hemochromatosis.[142] Obesity,[143] diabetes,[144] steatosis,[144] smoking,[145] oral contraceptive use,[146] and inadequate intake of selenium[147] and antioxidants[148] also have been implicated as risk factors. High incidence rates and young age of onset in sub-Saharan Africa and eastern and southeastern Asia are primarily a result of HBV infection acquired at birth or during childhood and are also a result of high consumption of aflatoxins.[140] Doubling of liver cancer incidence rates in the United States and other developed countries over the past 30 years (Fig 5) is in part attributed to chronic HCV infection that occurred in the 1960s and 1970s.[149,150]

Large-scale immunization against HBV at birth is the most important step to prevent liver cancer worldwide. In 1992, the World Health Organization recommended that hepatitis B vaccine be integrated into the immunization program of all countries by 1997, and currently over 135 countries have done so.[151] Decreasing aflatoxin exposure will likely reduce the incidence of liver cancer and has already contributed to the decrease in incidence in Singapore (Figs 3 and 4) and Shanghai, China over the past two decades.[88] Screening blood products for HBV and HCV, moderating alcohol consumption, and maintaining normal body weight are also important measures to reduce liver cancer incidence rates.

Cervical Cancer

With 493,100 new cases per year, cervical cancer in the seventh most common cancer in the world, and the second most common cancer among women (Fig 2). During the years 1973 and 1997, cervical cancer rates decreased in most parts of the world included in this study (Fig 4). Incidence rates are almost two-fold higher in less-developed compared with more-developed countries, 19.1 and 10.3 per 100,000 PY, respectively (Table 1). Incidence was highest in Africa and Central/South America (approximately 29 per 100,000 PY) and lowest in Oceania and North America (approximately 7.5 per 100,000 PY; Table 1). Mortality rates vary more than 10-fold across continents and therefore MR:IRs range from 0.27 in Oceania to 0.79 in Africa (Table 1).

Almost all cervical cancer cases are caused by one of 15 types of oncogenic human papillomavirus (HPV), with HPV types 16 and 18, accounting for the majority of cervical cancer cases.[152-154] Other suggested etiologic cofactors include low socioeconomic status,[155,156] smoking,[157,158] low intake of vitamins and micronutrients,[159,160] multiple sexual partners, promiscuous sexual partner,[152] sexual relations at a young age,[152] and oral contraceptive use.[157,158] The presence of HPV infection is a sine qua non in cervical carcinogenesis, and most other factors mediate their effect via exposure to HPV or by affecting susceptibility to the carcinogenic effects of HPV.

Low incidence and mortality rates of cervical cancer in more-developed countries have been attributed to extensive cancer screening practices. Age-specific incidence rates (Fig 5) reveal unique patterns: in more-developed countries rates are high in younger individuals but plateau after the age 40; in less-developed countries, rates are low at young ages but subsequently increase and, after age 40 years, exceed those in more-developed countries. The pattern in more-developed countries may in part be attributed to screening practices.

The conventional method of cervical cancer screening with Papanicolau smears involves sequential testing and is difficult to ubiquitously implement in developing countries due to requirement for compliance with repeated testing, expertise in specimen preparation and diagnostic interpretation, and cost. However, new studies using computer-based models have suggested that HPV DNA testing once (at age 35) or twice (at ages 35 and 40) can be used as a cost-effective method to reduce cervical cancer rates in developing countries.[161,162]

Creation of papillomavirus-like particles in the laboratory in the early 1990s[163] made it possible to make and test anti-HPV vaccines, which have already shown nearly 100% efficacy in reducing HPV infection and cancer rates.[164,165] In the near future, widespread vaccination against oncogenic types of HPV may significantly reduce the global burden of cervical cancer.[161]

Esophageal Cancer

Esophageal cancer is the eighth most common cancer in the world (Fig 2). Overall incidence rates are two-fold higher in less-developed compared with more-developed geographic regions, with the highest rates occurring in Asia (Table 1). Incidence and mortality rates are two- to three-fold higher in males than females. Survival is universally poor as reflected in high MR:IR worldwide (Table 1). Incidence rates rise steadily with advancing age in more-developed and less-developed areas, and incidence patterns are similar between both sexes (Fig 5). However, between 1973 and 1997, regional temporal trends varied, likely reflecting differences in underlying histologic subtypes. Squamous cell carcinoma of the esophagus (ESCC) comprises the majority of cases worldwide followed by adenocarcinoma of the esophagus (EAC).[166] Whereas ESCC incidence has decreased over the past three decades in more-developed countries where annual incidence rates are generally less than 10 per 100,000 PY,[116] incidence has remained high in some less-developed countries, where incidence rates can exceed 100 per 100,000 PY, particularly in high-risk areas of China,[167] Iran,[168,169] and South Africa.[170]

Smoking and alcohol consumption are strong risk factors for ESCC, especially in Western countries.[171-173] In the United States, where ESCC is more common among Blacks,[116] more than 90% of cases are attributed to smoking and alcohol consumption.[171,172] In contrast, few cases in high-risk areas of less-developed countries[168,174] are attributed to smoking and alcohol consumption, and purported risk factors include low consumption of fruits and vegetables,[175,176] selenium[177] and zinc deficiencies,[178] vitamin E deficiency,[179] high exposure to polycyclic aromatic hydrocarbons,[180] and poor oral hygiene.[181,182]

In contrast to ESCC, EAC predominantly occurs in more-developed countries, with the rate of rise in incidence exceeding the rate of decline of ESCC in several Western countries, in both males and females.[116,183] A rare entity 30 years ago, EAC now constitutes approximately half of all esophageal cancer cases in Western countries,[116,117,184,185] reflecting the increasing prevalence of implicated risk factors, gastroesophageal reflux,[120] smoking,[186] and obesity.[187]

Eliminating risk factors that account for a majority of esophageal cancers,[118] including tobacco use, alcohol intake, low fruit and vegetable consumption, obesity, and gastroesophageal reflux, may result in lowering incidence rates. Developing a greater understanding of the etiology of ESCC in less-developed countries, in particular, is needed. Detection, continued surveillance and/or treatment of precursor lesions, such as squamous dysplasia in ESCC and Barrett's esophagus in EAC may decrease cancer burden, although surveillance and treatment measures are expensive and treatment is associated with morbidity and mortality. Chemopreventive agents need additional study but have shown promise for prevention of both ESCC[188-190] and EAC.[191,192]

CONCLUSION

Given our current state of knowledge, a variety of approaches can be used to reduce cancer disparities between countries, including primary and secondary prevention methods. Several effective primary prevention measures are possible due to identification of etiologic agents, including avoidance of tobacco for lung cancer prevention; eradication of *H pylori* for stomach cancer prevention; vaccination against HPV for cervical cancer prevention; and vaccination against HBV for liver cancer prevention. Indeed, an estimated 35% of overall cancer mortality has been attributed to only nine modifiable risk factors.[193] Identification of premalignant or precursor lesions through secondary prevention efforts with screening and early detection strategies has been possible, including mammography for breast cancer detection; FOBT, colonoscopy, and other tests for colorectal cancer detection; and prostate-specific antigen testing for prostate cancer detection. Notably not all screening tests have gained universal acceptance and more definitive information regarding effectiveness of testing is awaited from ongoing clinical trials. Although successful cancer therapies have been identified over the past 30 years, treatments are often toxic, expensive, and require highly trained staff and specialized facilities. Consequently, the most feasible methods to reduce global cancer disparities are to target etiologic factors and high-risk behaviors and to develop strategies for prevention.

REFERENCES

1. Trans-HHS Cancer Health Disparities Progress Review Group: Making cancer health disparities history. U.S. Department of Health and Human Services, 2004

2. Carter-Pokras O, Baquet C: What is a "health disparity"? Public Health Rep 117:426-434, 2002

3. Last JM: A Dictionary of Epidemiology (3rd Ed). Oxford, Oxford University Press, 1995

4. Ferlay J, Bray F, Pisani P, et al: GLOBOCAN 2002, Cancer incidence, mortality and prevalence worldwide, IARC CancerBase No. 5, version 2.0, IARC Press. Lyon, France. http://www-dep.iarc.fr/globocan/database.htm

5. Parkin DM, Whelan SL, Ferlay J, et al: Cancer incidence in five continents, Vol VIII. Lyon, France, IARC Scientific Publications No. 155, 2002

6. Armitage P, Doll R: A two-stage theory of carcinogenesis in relation to the age distribution of human cancer. Br J Cancer 11:161-169, 1957

7. Armitage P, Doll R: The age distribution of cancer and a multi-stage theory of carcinogenesis. Br J Cancer 8:1-12, 1954

8. Devesa SS, Donaldson J, Fears T: Graphical presentation of trends in rates. Am J Epidemiol 141:300-304, 1995

9. Parkin DM, Whelan SL, Ferlay J, et al: Cancer incidence in five continents, I to VIII. Lyon, IARC Cancer Base No. 7, 2005

10. Parkin DM, Bray F, Ferlay J, et al: Global cancer statistics, 2002. CA Cancer J Clin 55:74-108, 2005

11. Jemal A, Ward E, Thun MJ: Contemporary lung cancer trends among U.S. women. Cancer Epidemiol Biomarkers Prev 14:582-585, 2005

12. Bertram JS: The molecular biology of cancer. Mol Aspects Med 21:167-223, 2000

13. Ashley DJ: The two "hit" and multiple "hit" theories of carcinogenesis. Br J Cancer 23:313-328, 1969

14. Fearon ER, Vogelstein B: A genetic model for colorectal tumorigenesis. Cell 61:759-767, 1990

15. Ezzati M, Lopez AD: Estimates of global mortality attributable to smoking in 2000. Lancet 362:847-852, 2003

16. Alberg AJ, Samet JM: Epidemiology of lung cancer. Chest 123:21S-49S, 2003

17. Wardwell NR, Massion PP: Novel strategies for the early detection and prevention of lung cancer. Semin Oncol 32:259-268, 2005

18. Alberg AJ, Brock MV, Samet JM: Epidemiology of lung cancer: Looking to the future. J Clin Oncol 23:3175-3185, 2005

19. Yang G, Fan L, Tan J, et al: Smoking in China: Findings of the 1996 National Prevalence Survey. JAMA 282:1247-1253, 1999

20. Warner KE: The role of research in international tobacco control. Am J Public Health 95:976-984, 2005

21. Ries LAG, Eisner MP, Kosary CL, et al: SEER Cancer Statistics Review, 1975-2002, National

Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2002/sections.html

22. Hirsch FR, Lippman SM: Advances in the biology of lung cancer chemoprevention. J Clin Oncol 23:3186-3197, 2005

23. Mulshine JL: New developments in lung cancer screening. J Clin Oncol 23:3198-3202, 2005

24. Roemer R, Taylor A, Lariviere J: Origins of the WHO framework convention on tobacco control. Am J Public Health 95:936-938, 2005

25. WHO framework convention on tobacco control (WHA56.1), Fifty-six World Health Assembly (agenda item 13), 2003

26. Henderson BE, Feigelson HS: Hormonal carcinogenesis. Carcinogenesis 21:427-433, 2000

27. Lilienfeld AM, Johnson EA: The age distribution in female breast and genital cancers. Cancer 8:875-882, 1955

28. Clemmesen J: Carcinoma of the breast. Br J Radiol 21:583-590, 1948

29. Thomas DB: Breast cancer in men. Epidemiol Rev 15:220-231, 1993

30. Anderson WF, Althuis MD, Brinton LA, et al: Is male breast cancer similar or different than female breast cancer? Breast Cancer Res Treat 83:77-86, 2004

31. Parkin DM, Bray FI, Devesa SS: Cancer burden in the year 2000: The global picture. Eur J Cancer 37:S4-66, 2001 (suppl 8)

32. Stevens RG, Moolgavkar SH, Lee JA: Temporal trends in breast cancer. Am J Epidemiol 115: 759-777, 1982

33. Anderson WF: Puberty and genetic susceptibility to breast cancer. N Engl J Med 349:1088-1089, 2003

34. Anderson WF, Chatterjee N, Ershler WB, et al: Estrogen receptor breast cancer phenotypes in the Surveillance, Epidemiology, and End Results database. Breast Cancer Res Treat 76:27-36, 2002

35. Yasui Y, Potter JD: The shape of age-incidence curves of female breast cancer by hormone-receptor status. Cancer Causes Control 10:431-437, 1999

36. Tarone RE, Chu KC: The greater impact of menopause on ER- than ER+ breast cancer incidence: A possible explanation (United States). Cancer Causes Control 13:7-14, 2002

37. Perou CM, Sorlie T, Eisen MB, et al: Molecular portraits of human breast tumours. Nature 406: 747-752, 2000

38. Moolgavkar SH, Lee JA, Hade RD: Comparison of age-specific mortality from breast cancer in males in the United States and Japan. J Natl Cancer Inst 60:1223-1225, 1978

39. Spratt JS Jr, Kaltenbach ML, Spratt JA: Cytokinetic definition of acute and chronic breast cancer. Cancer Res 37:226-230, 1977

40. Ershler WB: A gerontologist's perspective on cancer biology and treatment. Cancer Control 1:103-107, 1994

41. De Waard F, De Laive JWJ, Baanders-van Halewijn EA: On bimodal age distribution of mammary carcinoma. Br J Cancer 14:437-448, 1960

42. Anderson WF, Chu KC, Chang S, et al: Comparison of age-specific incidence rate patterns for different histopathologic types of breast carcinoma. Cancer Epidemiol Biomarkers Prev 13:1128-1135, 2004

43. Stalsberg H, Thomas DB: Age distribution of histologic types of breast carcinoma. Int J Cancer 54:1-7, 1993

44. Stalsberg H, Thomas DB, Noonan EA: Histologic types of breast carcinoma in relation to international variation and breast cancer risk factors. WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Int J Cancer 44:399-409, 1989

45. Putti TC, El-Rehim DM, Rakha EA, et al: Estrogen receptor-negative breast carcinomas: A review of morphology and immunophenotypical analysis. Mod Pathol 18:26-35, 2005

46. Armes JE, Egan AJ, Southey MC, et al: The histologic phenotypes of breast carcinoma occurring before age 40 years in women with and without BRCA1 or BRCA2 germline mutations: A population-based study. Cancer 83:2335-2345, 1998

47. Ashida A, Fukutomi T, Tsuda H, et al: Atypical medullary carcinoma of the breast with cartilaginous metaplasia in a patient with a BRCA1 germline mutation. Jpn J Clin Oncol 30:30-32, 2000

48. Hedenfalk I, Duggan D, Chen Y, et al: Gene-expression profiles in hereditary breast cancer. N Engl J Med 344:539-548, 2001

49. Breast Cancer Linkage Consortium: Pathology of familial breast cancer: Differences between breast cancers in carriers of BRCA1 or BRCA2 mutations and sporadic cases. Lancet 349:1505-1510, 1997

50. Johannsson OT, Idvall I, Anderson C, et al: Tumour biological features of BRCA1-induced breast and ovarian cancer. Eur J Cancer 33:362-371, 1997

51. Karp SE, Tonin PN, Begin LR, et al: Influence of BRCA1 mutations on nuclear grade and estrogen receptor status of breast carcinoma in Ashkenazi Jewish women. Cancer 80:435-441, 1997

52. Lakhani SR, Gusterson BA, Jacquemier J, et al: The pathology of familial breast cancer: Histological features of cancers in families not attributable to mutations in BRCA1 or BRCA2. Clin Cancer Res 6:782-789, 2000

53. Lakhani SR, Jacquemier J, Sloane JP, et al: Multifactorial analysis of differences between sporadic breast cancers and cancers involving BRCA1 and BRCA2 mutations. J Natl Cancer Inst 90:1138-1145, 1998

54. Marcus JN, Page DL, Watson P, et al: BRCA1 and BRCA2 hereditary breast carcinoma phenotypes. Cancer 80:543-556, 1997

55. Robson M, Gilewski T, Haas B, et al: BRCA-associated breast cancer in young women. J Clin Oncol 16:1642-1649, 1998

56. Verhoog LC, Brekelmans CT, Seynaeve C, et al: Survival and tumour characteristics of breast-cancer patients with germline mutations of BRCA1. Lancet 351:316-321, 1998

57. Marcus JN, Watson P, Page DL, et al: Hereditary breast cancer: Pathobiology, prognosis, and BRCA1 and BRCA2 gene linkage. Cancer 77:697-709, 1996

58. Eisinger F, Jacquemier J, Charpin C, et al: Mutations at BRCA1: the medullary breast carcinoma revisited. Cancer Res 58:1588-1592, 1998

59. Phillips KA: Breast carcinoma in carriers of BRCA1 or BRCA2 mutations: Implications of proposed distinct histologic phenotypes. Cancer 83: 2251-2254, 1998

60. Marcus JN, Watson P, Page DL, et al: BRCA2 hereditary breast cancer pathophenotype. Breast Cancer Res Treat 44:275-277, 1997

61. Armes JE, Venter DJ: The pathology of inherited breast cancer. Pathology 34:309-314, 2002

62. Chabon AB, Takeuchi S, Sommers SC: Histologic differences in breast carcinoma of Japanese and American women. Cancer 33:1577-1579, 1974

63. MacMahon B, Morrison AS, Ackerman LV, et al: Histologic characteristics of breast cancer in Boston and Tokyo. Int J Cancer 11:338-344, 1973

64. Morrison AS, Black MM, Lowe CR, et al: Some international differences in histology and survival in breast cancer. Int J Cancer 11:261-267, 1973

65. Rosen PP, Ashikari R, Thaler H, et al: A comparative study of some pathologic features of mammary carcinoma in Tokyo, Japan and New York, USA. Cancer 39:429-434, 1977

66. Amaku EO: A review of 40 cases of breast cancer seen in Lagos Teaching Hospital. West Afr Med J Niger Pract 17:102-104, 1968

67. Klonoff-Cohen HS, Schaffroth LB, Edelstein SL, et al: Breast cancer histology in Caucasians, African Americans, Hispanics, Asians, and Pacific Islanders. Ethn Health 3:189-198, 1998

68. Lawson JS, Field AS, Tran DD, et al: Breast cancer incidence and estrogen receptor alpha in normal mammary tissue: An epidemiologic study among Japanese women in Japan and Hawaii. Int J Cancer 97:685-687, 2002

69. Blanks RG, Moss SM, McGahan CE, et al: Effect of NHS breast screening programme on mortality from breast cancer in England and Wales, 1990-1998: Comparison of observed with predicted mortality. BMJ 321:665-669, 2000

70. Humphrey LL, Helfand M, Chan BK, et al: Breast cancer screening: A summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 137:347-360, 2002

71. Narod SA, Dube MP: Biologic characteristics of interval and screen-detected breast cancers. J Natl Cancer Inst 93:151-152, 2001

72. Porter PL, El-Bastawissi AY, Mandelson MT, et al: Breast tumor characteristics as predictors of mammographic detection: Comparison of interval- and screen-detected cancers. J Natl Cancer Inst 91:2020-2028, 1999

73. Gilliland FD, Joste N, Stauber PM, et al: Biologic characteristics of interval and screen-detected breast cancers. J Natl Cancer Inst 92:743-749, 2000

74. Fisher B, Costantino JP, Wickerham DL, et al: Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 90:1371-1388, 1998

75. Early Breast Cancer Trialists' Collaborative Group: Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. Lancet 365:1687-1717, 2005

76. Ries LAG, Eisner MP, Kosary CL, et al: SEER Cancer Statistics Review, 1975-2002, National Cancer Institute. Bethesda, MD, 2005

77. Vogelstein B, Fearon ER, Hamilton SR, et al: Genetic alterations during colorectal-tumor development. N Engl J Med 319:525-532, 1988

78. Day DW: The adenoma-carcinoma sequence. Scand J Gastroenterol Suppl 104:99-107, 1984

79. King H, Haenszel W: Cancer mortality among foreign- and native-born Chinese in the United States. J Chronic Dis 26:623-646, 1973

80. McMichael AJ, Giles GG: Cancer in migrants to Australia: Extending the descriptive epidemiological data. Cancer Res 48:751-756, 1988

81. McKeown-Eyssen GE: Fiber intake in different populations and colon cancer risk. Prev Med 16:532-539, 1987

82. Trock B, Lanza E, Greenwald P: Dietary fiber, vegetables, and colon cancer: Critical review and meta-analyses of the epidemiologic evidence. J Natl Cancer Inst 82:650-661, 1990

83. Slattery ML, Curtin KP, Edwards SL, et al: Plant foods, fiber, and rectal cancer. Am J Clin Nutr 79:274-281, 2004

84. Giovannucci E, Stampfer MJ, Colditz GA, et al: Multivitamin use, folate, and colon cancer in women in the Nurses' Health Study. Ann Intern Med 129:517-524, 1998

85. Chao A, Thun MJ, Connell CJ, et al: Meat consumption and risk of colorectal cancer. JAMA 293:172-182, 2005

86. Giovannucci E, Rimm EB, Stampfer MJ, et al: Intake of fat, meat, and fiber in relation to risk of colon cancer in men. Cancer Res 54:2390-2397, 1994

87. Schatzkin A, Lanza E, Corle D, et al: Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. Polyp Prevention Trial Study Group. N Engl J Med 342:1149-1155, 2000

88. Giovannucci E: Modifiable risk factors for colon cancer. Gastroenterol Clin North Am 31:925-943, 2002

89. Giovannucci E: Diet, body weight, and colorectal cancer: A summary of the epidemiologic evidence. J Womens Health 12:173-182, 2003

90. Samad AK, Taylor RS, Marshall T, et al: A meta-analysis of the association of physical activity with reduced risk of colorectal cancer. Colorectal Dis 7:204-213, 2005

91. Schnohr P, Gronbaek M, Petersen L, et al: Physical activity in leisure-time and risk of cancer: 14-year follow-up of 28,000 Danish men and women. Scand J Public Health 33:244-249, 2005

92. Brown ML, Potosky AL: The presidential effect: The public health response to media coverage about Ronald Reagan's colon cancer episode. Public Opin Q 54:317-329, 1990

93. Smith RA, von Eschenbach AC, Wender R, et al: American Cancer Society guidelines for the early detection of cancer: Update of early detection guidelines for prostate, colorectal, and endometrial cancers. Also: Update 2001–testing for early lung cancer detection. CA Cancer J Clin 51:38-75, 2001

94. Towler BP, Irwig L, Glasziou P, et al: Screening for colorectal cancer using the faecal occult blood test, hemoccult. Cochrane Database Syst Rev:CD001216, 2000

95. Kavanagh AM, Giovannucci EL, Fuchs CS, et al: Screening endoscopy and risk of colorectal cancer in United States men. Cancer Causes Control 9:455-462, 1998

96. Muller AD, Sonnenberg A: Protection by endoscopy against death from colorectal cancer: A case-control study among veterans. Arch Intern Med 155:1741-1748, 1995

97. Muller AD, Sonnenberg A: Prevention of colorectal cancer by flexible endoscopy and polypectomy: A case-control study of 32,702 veterans. Ann Intern Med 123:904-910, 1995

98. Newcomb PA, Norfleet RG, Storer BE, et al: Screening sigmoidoscopy and colorectal cancer mortality. J Natl Cancer Inst 84:1572-1575, 1992

99. Selby JV, Friedman GD, Quesenberry CP Jr, et al: A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. N Engl J Med 326:653-657, 1992

100. Hakama M, Hoff G, Kronborg O, et al: Screening for colorectal cancer. Acta Oncol 44:425-439, 2005

101. Hawk ET, Levin B: Colorectal cancer prevention. J Clin Oncol 23:378-391, 2005

102. Cunningham SC, Kamangar F, Kim MP, et al: Survival after gastric adenocarcinoma resection: Eighteen-year experience at a single institution. J Gastrointest Surg 9:718-725, 2005

103. Faycal J, Bessaguet C, Nousbaum JB, et al: Epidemiology and long term survival of gastric carcinoma in the French district of Finistere between 1984 and 1995. Gastroenterol Clin Biol 29:23-32, 2005

104. Tsubono Y, Hisamichi S: Screening for gastric cancer in Japan. Gastric Cancer 3:9-18, 2000

105. Roukos DH, Kappas AM: Perspectives in the treatment of gastric cancer. Nat Clin Pract Oncol 2:98-107, 2005

106. Helicobacter and Cancer Collaborative Group: Gastric cancer and Helicobacter pylori: A combined analysis of 12 case control studies nested within prospective cohorts. Gut 49:347-353, 2001

107. Smith GD, Hart C, Blane D, et al: Adverse socioeconomic conditions in childhood and cause specific adult mortality: Prospective observational study. Bmj 316:1631-1635, 1998

108. van Loon AJ, Brug J, Goldbohm RA, et al: Differences in cancer incidence and mortality among socio-economic groups. Scand J Soc Med 23:110-120, 1995

109. Tredaniel J, Boffetta P, Buiatti E, et al: Tobacco smoking and gastric cancer: Review and meta-analysis. Int J Cancer 72:565-573, 1997

110. Buiatti E, Palli D, Decarli A, et al: A case-control study of gastric cancer and diet in Italy. Int J Cancer 44:611-616, 1989

111. De Stefani E, Correa P, Boffetta P, et al: Dietary patterns and risk of gastric cancer: A case-control study in Uruguay. Gastric Cancer 7:211-220, 2004

112. Nouraie M, Pietinen P, Kamangar F, et al: Fruits, vegetables, and antioxidants and risk of gastric cancer among male smokers. Cancer Epidemiol Biomarkers Prev 14:2087-2092, 2005

113. Munoz N, Franceschi S: Epidemiology of gastric cancer and perspectives for prevention. Salud Publica Mex 39:318-330, 1997

114. Blot WJ, Devesa SS, Kneller RW, et al: Rising incidence of adenocarcinoma of the esophagus and gastric cardia. JAMA 265:1287-1289, 1991

115. Devesa SS, Fraumeni JF Jr: The rising incidence of gastric cardia cancer. J Natl Cancer Inst 91:747-749, 1999

116. Brown LM, Devesa SS: Epidemiologic trends in esophageal and gastric cancer in the United States. Surg Oncol Clin N Am 11:235-256, 2002

117. Devesa SS, Blot WJ, Fraumeni JF Jr: Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer 83: 2049-2053, 1998

118. Engel LS, Chow WH, Vaughan TL, et al: Population attributable risks of esophageal and gastric cancers. J Natl Cancer Inst 95:1404-1413, 2003

119. Lindblad M, Rodriguez LA, Lagergren J: Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric non-cardia adenocarcinoma among men and women in a nested case-control study. Cancer Causes Control 16:285-294, 2005

120. Lagergren J, Bergstrom R, Lindgren A, et al: Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 340:825-831, 1999

121. Dawsey SM, Mark SD, Taylor PR, et al: Gastric cancer and H pylori. Gut 51:457-458, 2002

122. Kolonel LN: Fat, meat, and prostate cancer. Epidemiol Rev 23:72-81, 2001

123. Chan JM, Gann PH, Giovannucci EL: Role of diet in prostate cancer development and progression. J Clin Oncol 23:8152-8160, 2005

124. Duffield-Lillico AJ, Dalkin BL, Reid ME, et al: Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: An analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial. BJU Int 91: 608-612, 2003

125. Clark LC, Dalkin B, Krongrad A, et al: Decreased incidence of prostate cancer with selenium supplementation: Results of a double-blind cancer prevention trial. Br J Urol 81:730-734, 1998

126. Giovannucci E: The epidemiology of vitamin D and cancer incidence and mortality: A review (United States). Cancer Causes Control 16:83-95, 2005

127. Virtamo J, Pietinen P, Huttunen JK, et al: Incidence of cancer and mortality following alpha-tocopherol and beta-carotene supplementation: A postintervention follow-up. JAMA 290:476-485, 2003

128. Weinstein SJ, Wright ME, Pietinen P, et al: Serum alpha-tocopherol and gamma-tocopherol in relation to prostate cancer risk in a prospective study. J Natl Cancer Inst 97:396-399, 2005

129. Giovannucci E: A review of epidemiologic studies of tomatoes, lycopene, and prostate cancer. Exp Biol Med 227:852-859, 2002

130. Leitzmann MF, Stampfer MJ, Michaud DS, et al: Dietary intake of n-3 and n-6 fatty acids and the risk of prostate cancer. Am J Clin Nutr 80:204-216, 2004

131. Freedland SJ: Obesity and prostate cancer: A growing problem. Clin Cancer Res 11:6763-6766, 2005

132. Haas GP, Sakr WA: Epidemiology of prostate cancer. CA Cancer J Clin 47:273-287, 1997

133. Breslow N, Chan CW, Dhom G, et al: Latent carcinoma of prostate at autopsy in seven areas. The International Agency for Research on Cancer, Lyons, France. Int J Cancer 20:680-688, 1977

134. Harris R, Lohr KN: Screening for prostate cancer: An update of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 137:917-929, 2002

135. Auvinen A, Curtis RE, Ron E: Risk of subsequent cancer following breast cancer in men. J Natl Cancer Inst 94:1330-1332, 2002

136. Kramer BS, Brown ML, Prorok PC, et al: Prostate cancer screening: What we know and what we need to know. Ann Intern Med 119:914-923, 1993

137. Lippman SM, Goodman PJ, Klein EA, et al: Designing the Selenium and Vitamin E Cancer Prevention Trial (SELECT). J Natl Cancer Inst 97:94-102, 2005

138. Lok AS: Prevention of hepatitis B virus-related hepatocellular carcinoma. Gastroenterology 127:S303-S309, 2004

139. Heathcote EJ: Prevention of hepatitis C virus-related hepatocellular carcinoma. Gastroenterology 127:S294-S302, 2004

140. Yu MC, Yuan JM: Environmental factors and risk for hepatocellular carcinoma. Gastroenterology 127:S72-S78, 2004

141. Morgan TR, Mandayam S, Jamal MM: Alcohol and hepatocellular carcinoma. Gastroenterology 127:S87-S96, 2004

142. Kowdley KV: Iron, hemochromatosis, and hepatocellular carcinoma. Gastroenterology 127: S79-S86, 2004

143. Caldwell SH, Crespo DM, Kang HS, et al: Obesity and hepatocellular carcinoma. Gastroenterology 127:S97-S103, 2004

144. Powell EE, Jonsson JR, Clouston AD: Steatosis: Co-factor in other liver diseases. Hepatology 42:5-13, 2005

145. Jee SH, Ohrr H, Sull JW, et al: Cigarette smoking, alcohol drinking, hepatitis B, and risk for hepatocellular carcinoma in Korea. J Natl Cancer Inst 96:1851-1856, 2004

146. Schlesselman JJ: Net effect of oral contraceptive use on the risk of cancer in women in the United States. Obstet Gynecol 85:793-801, 1995

147. Sakoda LC, Graubard BI, Evans AA, et al: Toenail selenium and risk of hepatocellular carcinoma mortality in Haimen City, China. Int J Cancer 115:618-624, 2005

148. Bjelakovic G, Nikolova D, Simonetti RG, et al: Antioxidant supplements for preventing gastrointestinal cancers. Cochrane Database Syst Rev: CD004183, 2004

149. Seeff LB: Introduction: The burden of hepatocellular carcinoma. Gastroenterology 127:S1-4, 2004

150. Hoofnagle JH: Hepatocellular carcinoma: Summary and recommendations. Gastroenterology 127:S319-S323, 2004

151. World Health Organization. Hepatitis B vaccine, http://www.who.int/vaccines/en/hepatitisb.shtml

152. Schiffman MH, Brinton LA, Devesa S, et al: Cervical cancer, in Schottenfeld D, Fraumeni JF Jr (eds): Cancer Epidemiology and Prevention. New York, Oxford University Press, 1996, pp 1090-1116

153. Bosch FX, de Sanjose S: Human papillomavirus and cervical cancer: Burden and assessment of causality. J Natl Cancer Inst Monogr 3-13, 2003

154. Munoz N, Bosch FX, de Sanjose S, et al: Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med 348:518-527, 2003

155. Fasal E, Simmons ME, Kampert JB: Factors associated wih high and low risk of cervical neoplasia. J Natl Cancer Inst 66:631-636, 1981

156. Brinton LA, Hamman RF, Huggins GR, et al: Sexual and reproductive risk factors for invasive squamous cell cervical cancer. J Natl Cancer Inst 79:23-30, 1987

157. Hellberg D, Stendahl U: The biological role of smoking, oral contraceptive use and endogenous sexual steroid hormones in invasive squamous epithelial cervical cancer. Anticancer Res 25:3041-3046, 2005

158. Castellsague X, Munoz N: Cofactors in human papillomavirus carcinogenesis: Role of parity, oral contraceptives, and tobacco smoking. J Natl Cancer Inst Monogr 20-28, 2003

159. Ziegler RG, Weinstein SJ, Fears TR: Nutritional and genetic inefficiencies in one-carbon metabolism and cervical cancer risk. J Nutr 132:2345S-2349S, 2002

160. Hernandez BY, McDuffie K, Wilkens LR, et al: Diet and premalignant lesions of the cervix: Evidence of a protective role for folate, riboflavin, thiamin, and vitamin B12. Cancer Causes Control 14:859-870, 2003

161. Schiffman M, Castle PE: The promise of global cervical-cancer prevention. N Engl J Med 353:2101-2104, 2005

162. Goldie SJ, Gaffikin L, Goldhaber-Fiebert JD, et al: Cost-effectiveness of cervical-cancer screening in five developing countries. N Engl J Med 353:2158-2168, 2005

163. Zhou J, Sun XY, Stenzel DJ, et al: Expression of vaccinia recombinant HPV 16 L1 and L2 ORF proteins in epithelial cells is sufficient for assembly of HPV virion-like particles. Virology 185:251-257, 1991

164. Koutsky LA, Ault KA, Wheeler CM, et al: A controlled trial of a human papillomavirus type 16 vaccine. N Engl J Med 347:1645-1651, 2002

165. Villa LL, Costa RL, Petta CA, et al: Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: A randomised double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncol 6:271-278, 2005

166. Stewart BW, Kleihues P: World Cancer Report. Lyon, IARC Press, 2003

167. Blot WJ, Li JY, Taylor PR, et al: Nutrition intervention trials in Linxian, China: Supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. J Natl Cancer Inst 85:1483-1492, 1993

168. Islami F, Kamangar F, Aghcheli K, et al: Epidemiologic features of upper gastrointestinal tract cancers in Northeastern Iran. Br J Cancer 90:1402-1406, 2004

169. Mahboubi E, Kmet J, Cook PJ, et al: Oesophageal cancer studies in the Caspian Littoral of Iran: The Caspian cancer registry. Br J Cancer 28:197-214, 1973

170. Somdyala NI, Marasas WF, Venter FS, et al: Cancer patterns in four districts of the Transkei region–1991-1995. S Afr Med J 93:144-148, 2003

171. Brown LM, Hoover RN, Greenberg RS, et al: Are racial differences in squamous cell esophageal cancer explained by alcohol and tobacco use? J Natl Cancer Inst 86:1340-1345, 1994

172. Brown LM, Hoover R, Silverman D, et al: Excess incidence of squamous cell esophageal cancer among US black men: Role of social class and other risk factors. Am J Epidemiol 153:114-122, 2001

173. Tuyns AJ: Oesophageal cancer in non-smoking drinkers and in non-drinking smokers. Int J Cancer 32:443-444, 1983

174. Tran GD, Sun XD, Abnet CC, et al: Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. Int J Cancer 113:456-463, 2005

175. Brown LM, Swanson CA, Gridley G, et al: Dietary factors and the risk of squamous cell esophageal cancer among black and white men in the United States. Cancer Causes Control 9:467-474, 1998

176. Cook-Mozaffari PJ, Azordegan F, Day NE, et al: Oesophageal cancer studies in the Caspian Littoral of Iran: Results of a case-control study. Br J Cancer 39:293-309, 1979

177. Mark SD, Qiao YL, Dawsey SM, et al: Prospective study of serum selenium levels and incident esophageal and gastric cancers. J Natl Cancer Inst 92:1753-1763, 2000

178. Abnet CC, Lai B, Qiao YL, et al: Zinc concentration in esophageal biopsy specimens measured by x-ray fluorescence and esophageal cancer risk. J Natl Cancer Inst 97:301-306, 2005

179. Taylor PR, Qiao YL, Abnet CC, et al: Prospective study of serum vitamin E levels and esophageal and gastric cancers. J Natl Cancer Inst 95:1414-1416, 2003

180. Kamangar F, Strickland PT, Pourshams A, et al: High exposure to polycyclic aromatic hydrocarbons may contribute to high risk of esophageal cancer in northeastern Iran. Anticancer Res 25:425-428, 2005

181. Abnet CC, Qiao YL, Mark SD, et al: Prospective study of tooth loss and incident esophageal and gastric cancers in China. Cancer Causes Control 12:847-854, 2001

182. Sepehr A, Kamangar F, Fahimi S, et al: Poor oral health as a risk factor for esophageal squamous dysplasia in northeastern Iran. Anticancer Res 25: 543-546, 2005

183. Vizcaino AP, Moreno V, Lambert R, et al: Time trends incidence of both major histologic types of esophageal carcinomas in selected countries, 1973-1995. Int J Cancer 99:860-868, 2002

184. Walther C, Zilling T, Perfekt R, et al: Increasing prevalence of adenocarcinoma of the oesophagus and gastro-oesophageal junction: A study of the Swedish population between 1970 and 1997. Eur J Surg 167:748-757, 2001

185. Wijnhoven BP, Louwman MW, Tilanus HW, et al: Increased incidence of adenocarcinomas at the gastro-oesophageal junction in Dutch males since the 1990s. Eur J Gastroenterol Hepatol 14:115-122, 2002

186. Gammon MD, Schoenberg JB, Ahsan H, et al: Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia. J Natl Cancer Inst 89:1277-1284, 1997

187. Chow WH, Blot WJ, Vaughan TL, et al: Body mass index and risk of adenocarcinomas of the esophagus and gastric cardia. J Natl Cancer Inst 90:150-155, 1998

188. Limburg PJ, Wei W, Ahnen DJ, et al: Randomized, placebo-controlled, esophageal squamous cell cancer chemoprevention trial of selenomethionine and celecoxib. Gastroenterology 129:863-873, 2005

189. Kresty LA, Morse MA, Morgan C, et al: Chemoprevention of esophageal tumorigenesis by dietary administration of lyophilized black raspberries. Cancer Res 61:6112-6119, 2001

190. Shimizu M, Suzui M, Deguchi A, et al: Effects of acyclic retinoid on growth, cell cycle control, epidermal growth factor receptor signaling, and gene expression in human squamous cell carcinoma cells. Clin Cancer Res 10:1130-1140, 2004

191. Vaughan TL, Dong LM, Blount PL, et al: Nonsteroidal anti-inflammatory drugs and risk of neoplastic progression in Barrett's oesophagus: A prospective study. http://oncology.thelancet.com, 2005

192. Raj A, Jankowski J: Acid suppression and chemoprevention in Barrett's oesophagus. Dig Dis 22:171-180, 2004

193. Danaei G, Vander Hoorn S, Lopez AD, et al: Causes of cancer in the world: Comparative risk assessment of nine behavioural and environmental risk factors. Lancet 366:1784-1793, 2005

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

Author Contributions

Conception and design: Farin Kamangar, Graça M. Dores, William F. Anderson
Provision of study materials or patients: Farin Kamangar, Graça M. Dores, William F. Anderson
Collection and assembly of data: Farin Kamangar, Graça M. Dores, William F. Anderson
Data analysis and interpretation: Farin Kamangar, Graça M. Dores, William F. Anderson
Manuscript writing: Farin Kamangar, Graça M. Dores, William F. Anderson
Final approval of manuscript: Farin Kamangar, Graça M. Dores, William F. Anderson